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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,513	08/06/2002	Peter Brossart	WWELL52.001APC	8680

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,513	BROSSART ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,15,21,24,27,29 and 31* is/are pending in the application.

4a) Of the above claim(s) *21,24,27,29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed October 7, 2004 in response to the Office Action of August 5, 2004 is acknowledged and has been entered. Previously pending claim 1 has been amended, claims 2-14, 16-20, 22-23, 25-26, 28, 30, 32-35 are canceled. Claims 1 and 15 are currently being examined.

2. Applicant submits that claims 1 and 15 are now in allowable condition and request rejoinder of claims 21, 24, 27, 29 and 31 which depend from and contain all of the limitations of claim 1. The request has been considered but claims 21, 24, 27, 29 and 31 will not be rejoined with the elected group because claims 1 and 15 are not allowable for the reasons set forth below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection

4. The specification is objected to repeatedly misspelling the term "adjuvant" as "adjuvans". Appropriate correction is required.

The specification is objected to in the use of the term "galenicals" on page 9. This is not a term used in the art and its meaning is unknown. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 15 are rejected under 35 USC 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an isolated peptide consisting of SEQ ID NO:1 (claim 1), a pharmaceutical composition comprising the isolated peptide of claim 1 (claim 15). It is noted that inherent to pharmaceutical compositions is the *in vivo* use thereof for, at least in this case, the treatment of disease.

The specification teaches that the invention relates to a peptide that is derived from the MUC-1 gene, by which peptide a HLA-A2-restricted immune reaction against tumor cells can be triggered (p. 1, first paragraph). MUC-1 on normal cells is not normally accessible to the immune system, whereas MUC-1 on tumor cells is accessible due to incomplete glycosylation (page 3). For triggering an effective T cell immune reaction, co-stimulators are required. Included in this class of helpers are dendritic cells which take up proteins and present them so that cytotoxic T cells can be activated (page 4). The known amino acid sequence of MUC-1 was searched for HLA-A2 binding motifs by computer analysis. High binding probability sequences, including SEQ ID NO:1, were identified, synthesized and examined for their ability to induce cytotoxic T cells *in vitro* with the help of dendritic cells (page 5). The specification exemplifies the induction of cytotoxic T cells against tumor cells *in vitro*, wherein the cytotoxic T cells are stimulated by dendritic cells presenting SEQ ID NO:1 (p. 6 and see examples), thus this peptide offers the possibility of an effective tumor therapy in which the suppression of an immune reaction against tumor cells often observed in tumor

patients can be reversed (pages 5-6). The specification teaches that a pharmaceutical composition is a composition which comprises a peptide in an amount which is sufficient for triggering an MHC-1-restricted immune response (p. 9). In the case of peptides, these preparations are usually used for vaccinations and contain an adjuvant. By means of an appropriate pharmaceutical preparation, it is possible to treat organisms directly without having to pretreat antigen presenting cells (p. 9). Thus it is clear from the teaching of the specification as originally filed that the claimed invention is drawn to a peptide to be used for the treatment of cancer's expressing immune-system accessible MUC-1.

One cannot extrapolate the teaching of the specification to the enablement of the claims because the prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al (International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary

tumors *in situ* are often heterogeneous with respect to MHC presentation. The effect of the claimed pharmaceutical composition upon such a heterogenous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules. The specification demonstrates that SEQ ID NO:1, when presented by dendritic cells, induces cytotoxic T cells *in vitro* which were able to specifically lyse tumor cell line cells that express HLA-A2 and MUC-1 but not cell lines which do not express MUC-1. However, this is not sufficient to enable the claimed invention because it cannot be predicted that the claimed peptide or pharmaceutical composition would in fact be effective to treat cancer, as contemplated, by HLA-restricted stimulation of a T-cell response against a tumor. Although the specification teaches that for triggering an effective T cell immune reaction, co-stimulators are required, the claimed pharmaceutical composition does not include the suggested co-stimulators. Although the specification also teaches that by means of an appropriate pharmaceutical preparation it is possible to treat organisms directly without having to pretreat antigen presenting cells, the specification provides no guidance on what the "appropriate" pharmaceutical preparation might be. In particular, Lee et al (J. Immunol., 1999, 163:6292-6300), specifically teach that although a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, this response does not associate with a clinically evident regression of metastatic melanoma (see abstract). Further, Kirkin et al (1998, APMIS, 106 : 665-679) teach

that in particular for tumor antigens, for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). It is noted that Brossart et al (Blood, 1999, 93:4309-4317, IDS item) specifically teach that both immunosupression and MUC1 tolerance in cancer patients is well known in the art (p. 4315, col 2). Further, Chaux et al, (Int J Cancer, 1998, 77: 538-542) teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* condition in which the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Given the above, even if a peptide on a cell line cell was recognized by T-cells *in vitro*, it could not be predicted that the T-cells would recognize these peptides *in vivo* and if not recognized *in vivo*, it is clear that one would not know how to use the claimed peptide. Similarly Sherman et al, (Critical Reviews in Immunol, 1998, 18:47-54) teach that self-tolerance may eliminate T cells that are capable of recognizing T-cell epitopes with high avidity . Smith (Clin Immunol, 1994, 41(4): 841-849), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484).. In particular as drawn to the peptide itself, Bossart et al, *Supra* are very clear that immunization methods using self-antigens have often resulted in the induction of low-affinity CTL responses and consequently a lack of sufficient recognition of naturally processed

antigens by these CTL. Presentation of antigens by APC may be critical for the effectiveness of an induced immune response (p. 4309, col 1). Bossart et al, *Supra* conclude with the hypothesis that "The use of DC-**and** MUC1-derived peptides **could** (emphasis added) reverse the observed immunosuppression and MUC1 tolerance in cancer patients." However, given the teachings set forth above and the known state of the art at the time the invention was made, one would not believe it more likely than not that the claimed pharmaceutical composition would function as claimed. Given that the only use taught for the claimed peptide is for the treatment of cancer wherein an effective anti-cancer T-cell response is elicited, one would not know how to use the claimed peptide.

In addition, as drawn to cancer vaccines, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred (and is clearly known for MUC1 as set forth above) and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph) as also set forth above. Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy, as contemplated, could be induced by the peptide of the invention in patients having tumor burden. In addition, as drawn to peptide tumor vaccines for the induction of a T-cell response, Kirkin et al, *Supra* review several

melanoma-associated antigens, including NY-ESO1, and conclude that initiation of a strong immune response *in vivo* is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et al teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL *in vitro*, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response *in vivo*, only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, *Supra*. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as claimed or as contemplated with a reasonable expectation of success. Given the unpredictability that the pharmaceutical composition comprising SEQ ID NO:1 would elicit an adequate T cell response *in vivo*, useful for the treatment of cancer as contemplated, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention. Further, given the above, since the only use contemplated in the specification for the claimed peptide is in the T-cell stimulated treatment/prophylaxis of cancer, one would not know how to use the claimed peptide.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention

7. All other objections and rejections recited in the paper mailed August 5, 2004 are hereby withdrawn.

8. No claims allowed.

9. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

> A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Susan Ungar
Primary Patent Examiner
December 14, 2004